JUSTIFICATION AND RATIONALE FOR INTERVENTIONS IN MEDIA FILL

ASEPTIC ASSEMBLY OF FILLING MACHINE PARTS

- **Intervention type:** Routine intervention.
- **Duration of time:** Assembling shall be performed for 3 hours.
- **Process application:** Solution, suspension, bulk sterilization and process related to Brinzolamide product.
- **Filling Machine door no. to be opened during intervention:** E/FD-001, E/FD-002, E/FD-004, E/FD-005, E/FD-007, E/FD-008, E/F-009, E/FD-010, E/FD-011, E/FD-012, E/FD-014, E/D-015. Door of filling machine to be opened, according to the activity and two filling machine guard doors shall be kept open maximum for 20 minutes during assembling.
- **Frequency:** Shall be performed one time at the start of filling.
- **Activity perform during intervention:** During aseptic assembling of filling machine parts perform the activity in filling room under LAF, aseptic assembling activity shall be performed one time at the start of filling and filling machine guard door shall be kept open two side maximum for 20 minutes during assembling.
- **Rationale:**
- The duration of process simulation of Guard door open should generally be not less than the actual production process to be best simulate contamination risk introduced by door opening and during assembling of sterilized machine parts.
- Based upon the trend of 10 production and 10 media fill batches data obtained, it is proposed to complete the assembling activity within 3 hours .further this maximum time of 3 hours is to be simulated during the media fill batch and evaluate the risk in the production process.

ADDITION OF BOTTLES IN BOTTLE VIBRATORY HOPPER

- **Intervention type:** Routine intervention.
- **During of time:** Shall be performed 2 minutes at a stretch.
- **Process application:** Solution, suspension, bulk sterilization and process related to Brinzolamide product.
- **Frequency:** Shall be perform at least 128 times in solution, suspension and bulk sterilization process 56 times in process related to Brinzolamide product.
- **Activity performs during intervention:** Addition of bottles in bottle vibratory hopper, poly bags of bottles cut with sterile cutter and the bottle under LAF in respective bottle vibratory hopper. One bag of bottle to be handled 4 times of addition of bottles inside the respective hopper (as application to batch size) so, request frequency of intervention with respect to maximum commercial batch size of product filling to be simulated in media fill.
- **Rationale:**

✓ The duration of process simulation should generally be not less than the actual production process to best simulate the contamination risk introduced to the filling activity during addition of pre sterilized in the vibratory hopper.

✓ Based upon the trend of 10 media fill batches data obtained, it is found that the bottle charging activity takes 2 minutes. This charging activity is performed under LAF but the contamination risk cannot be overruled considering the number of times the activity is performed during filling. Hence, to simulate the number of times of bottle addition is done during product batch filling, maximum of 128 for solution, suspension and bulk sterilization and 56 times for process related to brinzolamide product is to be performed during media fill. These numbers are evaluated based on product maximum batch size on the filling line. Refer bellow details for further justification process wise.

- **Fore solution, suspension, bulk sterilization process:**

Maximum product batch size for 5 ml pack size 300 liters and 10 ml pack size is 600 liters and maximum batch size of solution media fill is 80 liters of 5 ml pack size and 160 liters for 10 ml pack size is 160 liters.

✓ For solution product maximum bottle issued 58000 units and in media fill maximum bottle issued quantity is 16667 units.

✓ One packet or poly bag contains 500 presterilized bottles of 5 ml and/or 10 ml.

✓ Actual product batch size is 58000 nos. and considering additional 10% quantity as overage total bottle quantity issued is 64000 units.

One packet contains 500 units so, number of times intervention to be simulated is 64000/500 = 128.

- **For Brinzolamide process:** Arbitrarily, batch size of Brinzolamide product is considered 12000 units for 10 ml and 12000 units of 15 ml packs. Till data Brinzolamide product taken with much lesser batch size than the proposed batch size of 12000 units.
    - ✓ One pack of 10 ml bottle contains 500 units, number of times intervention to be performed is 12000/500 = 24 times and 15 ml pack , number of times intervention to be performed is 12000/375 = 32
    - ✓ So, total 56 times bottle charging intervention to be simulated during media fill.

CORRECTION OF BOTTLE BLOCKAGE IN BOTTLE VIBRATORY SORTING BOWL

- **Intervention type:** Routine intervention.
- **Duration of time:** Shall be performed for maximum 2 minutes.
- **Process applicable:** Solution, suspension, bulk sterilization and process related to Brinzolamide product.
- **Frequency:** Shall be perform at last 5 times in solution, suspension, bulk sterilization process and 6 times for process related to Brinzolamide product.
- **Filling machine door no. to be opened during intervention:** E/FD-002 and E/FD-014.
- **Activity to be performed during intervention:** Guard door E/FD-002 and E/FD/-014 has to be opened, hand sanitization to be done, blocked bottles to be cleared with the help of sterilized forceps in bottle vibratory sorting bowl.
- **Rationale:**
    - ✓ The duration of process simulation should generally be not less than the actual production process to best simulate the contamination risk introduced to the filling activity during addition of pre sterilized bottles in the vibratory hopper.
    - ✓ Based upon the trend of 10 media fill batches data obtained, it is proposed to complete the bottle blockage clearing activity within 2 minutes. Based on the proposed maximum production batch size number of times is finalized to simulate during media fill.

CORRECTION OF BOTTLE BLOCKAGE IN BOTTLE CHUTE

- **Intervention type:** Routine intervention.
- **Duration of time:** Shall be performed for maximum 3 minutes.
- **Process applicable:** Solution, suspension, bulk sterilization and process related to Brinzolamide product.
- **Frequency:** Shall be performed at least10 times in solution, suspension, bulk sterilization and 6 times in process related to Brinzolamide product.
- **Filling machine door no. to be opened during intervention:** NA
- **Activity perform during intervention:** This intervention is to be executed through glove port with the sterile forceps kept under LAF.
- **Rationale:** During review of filling process this new type of intervention is identified and proposed to be simulated during the media fill. Contamination risk of this intervention in the filling process will be evaluated with the number of times proposed.

CORRECTION OF BOTTLE BLOCKAGE AT IN-FEED GUIDE OF BOTTLE

- **Intervention type:** Routine intervention.
- **Duration of time:** Shall be performed for maximum 3 minutes.
- **Process applicable:** Solution, suspension, bulk sterilization and process related to Brinzolamide product.
- **Frequency:** Shall be performed at least 5 times in solution, suspension, bulk sterilization and 6 times in process related to Brinzolamide product.
- **Filling machine door no. to be opened during intervention:** NA
- **Activity perform during intervention:** This intervention is to be executed through glove port with the sterile forceps kept under LAF.
- **Rationale:**

    - ✓ The duration of process simulation should generally be not less than the actual production process to best simulate the contamination risk introduced to the filling activity during clearing the bottle blockage at in-feed guide of bottle.

- ✓ Based upon the trend of 10 media fill batches and 10 production batches data obtained, it is proposed to complete the bottle blockage clearing activity within 3 minutes. Based on the proposed maximum production batch size number of times is finalized to simulate during media fill.

REMOVAL OF FALLEN BOTTLES ON WALKING BEAM FROM DISCHARGE CHUTE

- **Intervention type:** Routine intervention.
- **Duration of time:** Shall be performed for maximum 3 minutes.
- **Process applicable:** Solution, suspension, bulk sterilization and process related to Brinzolamide product.
- **Frequency:** Shall be performed at least 5 times in solution, suspension, bulk sterilization and 6 times in process related to Brinzolamide product.
- **Filling machine door no. to be opened during intervention:** NA
- **Activity performs during intervention:** This intervention is to be executed through glove port with the sterile forceps kept under LAF.
- **Rationale:**
  - ✓ The duration of process simulation should generally be not less than the actual production process to best simulate the contamination risk introduced to the filling activity during removal of fallen bottles on walking beam from discharge chute.
  - ✓ Based upon the trend of 10 media fill batches and 10 production batches data obtained, it is proposed to complete the intervention removal of fallen bottles on walking beam from discharge chute within 3 minutes. Based on the proposed maximum production batch size number of times is finalized to simulate during media fill.

REMOVAL OF JAMMED FILLED AND CAPPED BOTTLE AT OUT FEED OF CAPPING MACHINE

- **Intervention type:** Routine intervention.
- **Duration of time:** Shall be performed for maximum 3 minutes.
- **Process applicable:** Solution, suspension, bulk sterilization and process related to Brinzolamide product.
- **Frequency:** Shall be performed at least 10 times in solution, suspension, bulk sterilization and 6 times in process related to Brinzolamide product.
- **Filling machine door no. to be opened during intervention:** NA
- **Activity performs during intervention:** This intervention is to be executed through glove ports with the sterile forceps kept under LAF.
- **Rationale:** As suggested by regulatory inspector, earlier this intervention was not simulated during media fill and the impact of this intervention on production batch was not evaluated. Hence, this new type of intervention is identified and proposed to be simulated during the media fill. Contamination risk of this intervention in the filling process will be evaluated with the number of times to bracket the entire filling activity.

ADDITION OF DROPPERS AT DROPPER VIBRATORY HOPPER

- **Intervention type:** Routine intervention.
- **Duration of time:** Shall be performed for maximum 2 minutes.
- **Process applicable:** Solution, suspension, bulk sterilization and process related to Brinzolamide product.
- **Frequency:** Shall be performed at least 22 times in solution, suspension, bulk sterilization and 8 times for process related to Brinzolamide product.
- **Filling machine door no. to be opened during intervention:** E/FD-011
- **Activity performs during intervention:** Hand sanitization to be done, guard door no. E/FD-011 to be opened and intervention of droppers after cutting the pack with sterilized cutter to be done in the vibratory hopper, finally filling machine guard door E/FD-011 to be closed.
- **Rationale:**
  - ✓ The duration of process simulation should generally be not less than the actual production process to best simulate the contamination risk introduced to the filling activity during addition of dropper in the vibratory hopper.

- ✓ Based upon the trend of 10 media fill batches and 10 production batches data obtained, it is proposed to complete the intervention addition of dropper in the vibratory hopper within 2 minutes. Based on the proposed maximum production batch size number of times is finalized to simulate during media fill.

❖ **For solution, suspension, bulk sterilization process:**

Maximum product batch size for 5 ml size is 300 liters and for 10 ml pack size is 600 liters and maximum batch size of solution media fill is 80 liters for 5 ml pack size and 160 liters for 10 ml pack size is 160 liters.

- ✓ For solution product maximum dropper issued 58000 units and in media fill maximum dropper issued quantity is 16667 units.
- ✓ One pack or poly bag contains 3000 pre sterilized droppers for 5 ml and/or 10 ml.
- ✓ Actual product batch size is 58000 nos. and considering additional 10% quantity as overage total dropper quantity issued is 64000 units.

One packet contains 3000 units so, number of times intervention to be simulated is

64000/3000 = 22 times.

❖ **For Brinzolamide process:** Arbitrarily, batch size of brinzolamide product is considered 12000 units for 10 ml and 12000 units of 150ml packs. Till date brinzolamide product taken with much lesser batch size than the proposed batch size of 12000 units.

- ✓ One pack of droppers for 3000 units, so number of times intervention to be performed is 24000/3000 = 8 times.

9. Addition of caps at cap vibratory hopper.

❖ **Intervention type:** Routine intervention.
❖ **Duration of time:** Shall be performed for maximum 2 minutes.
❖ **Process applicable:** Solution, suspension, bulk sterilization and process related Brinzolamide product.
❖ **Frequency:** Shall be performed at least 64 times in solution, suspension, bulk sterilization and at least 26 times for process related to Brinzolamide product.
❖ **Filling machine door no. to be opened during intervention:** E/FD-009 and E/FD-010
❖ **Activity performs during intervention:** Hand sanitization to be done, guard door no. E/FD-009 and E/FD-010 to be opened and intervention of addition droppers after cutting the pack with sterilized cutter to be done in the vibratory hopper, finally filling machine guard door E/FD-009 and E/FD -010 to be closed.
❖ **Rationale:**
- ✓ The duration of process simulation should generally be not less than the actual production process to best simulate the contamination risk introduced to the filling activity during addition of caps in the vibratory hopper.
- ✓ Based upon the trend of 10 media fill batches and 10 production batches data obtained, it is proposed to complete the intervention addition of caps in the vibratory hopper within 2 minutes. Based on the proposed maximum production batch size number of times is finalized to simulate during media fill.

❖ **For solution, suspension, bulk sterilization process:**

Maximum product batch size for 5 ml size is 300 liters and for 10 ml pack size is 600 liters and maximum batch size of solution media fill is 80 liters for 5 ml pack size and 160 liters for 10 ml pack size is 160 liters.

- ✓ For solution product maximum cap issued 58000 units and in media fill maximum cap issued quantity is 16667 units.
- ✓ One pack or poly bag contains 1000 pre sterilized cap for 5 ml and/or 10 ml.
- ✓ Actual product batch size is 58000 nos. and considering additional 10% quantity as overage total cap quantity issued is 64000 units.

One packet contains 1000 units so, number of times intervention to be simulated is

64000/1000 = 64 times.

❖ **For Brinzolamide process:** Arbitrarily, batch size of brinzolamide product is considered 12000 units for 10 ml and 12000 units of 15 ml packs. Till date brinzolamide product taken with much lesser batch size than

the proposed batch size of 12000 units. Considering the loss during processing 2 packet of cap is issued along with each batch.

One pack of cap for 1000 units, so number of times intervention to be performed is 26000/100 = 26 times.

10. CORRECTION OF DROPPER IN DROPPER VIBRATOERY BOWL.

- **Intervention type:** Routine intervention.
- **Duration of time:** Shall be performed for maximum 2 minutes.
- **Process applicable:** Solution, suspension, bulk sterilization and process related to Brinzolamide product.
- **Frequency:** Shall be performed at least10 times in solution, suspension, bulk sterilization and 6 times in process related to Brinzolamide product.
- **Filling machine door no. to be opened during intervention:** NA
- **Activity perform during intervention:** This intervention is to be executed through glove port with the sterile forceps kept under LAF.
- **Rationale:** During review of filling process this new type of intervention is identified and proposed to be simulated during the media fill. Contamination risk of this intervention in the filling process will be evaluated with the number of times proposed.

11. Correction of dropper movement in dropper chute.

- **Intervention type:** Routine intervention.
- **Duration of time:** Shall be performed for maximum 3 minutes.
- **Process applicable:** Solution, suspension, bulk sterilization and process related to Brinzolamide product.
- **Frequency:** Shall be performed at least10 times in solution, suspension, bulk sterilization and 6 times in process related to Brinzolamide product.
- **Filling machine door no. to be opened during intervention:** NA
- **Activity perform during intervention:** This intervention is to be executed through glove port with the sterile forceps kept under LAF.
- **Rationale:** During review of filling process this new type of intervention is identified and proposed to be simulated during the media fill. Contamination risk of this intervention in the filling process will be evaluated with the number of times proposed.

12. Correction of dropper in dropper pick and place assembly.

- **Intervention type:** Routine intervention.
- **Duration of time:** Shall be performed for maximum 3 minutes.
- **Process applicable:** Solution, suspension, bulk sterilization and process related to Brinzolamide product.
- **Frequency:** Shall be performed at least10 times in solution, suspension, bulk sterilization and 6 times in process related to Brinzolamide product.
- **Filling machine door no. to be opened during intervention:** NA
- **Activity perform during intervention:** This intervention is to be executed through glove port with the sterile forceps kept under LAF.
- **Rationale:** During review of filling process this new type of intervention is identified and proposed to be simulated during the media fill. Contamination risk of this intervention in the filling process will be evaluated with the number of times proposed.

13. Correction of cap movement in cap vibratory bowl.

- **Intervention type:** Routine intervention.
- **Duration of time:** Shall be performed for maximum 2 minutes.
- **Process applicable:** Solution, suspension, bulk sterilization and process related to Brinzolamide product.
- **Frequency:** Shall be performed at least 8 times in solution, suspension, bulk sterilization and 6 times in process related to Brinzolamide product.
- **Filling machine door no. to be opened during intervention:** NA
- **Activity perform during intervention:** This intervention is to be executed through glove port with the sterile forceps kept under LAF.
- **Rationale:** During review of filling process this new type of intervention is identified and proposed to be simulated during the media fill. Contamination risk of this intervention in the filling process will be evaluated with the number of times proposed.

14. Correction of cap movement in cap chute.

- **Intervention type:** Routine intervention.
- **Duration of time:** Shall be performed for maximum 3 minutes.
- **Process applicable:** Solution, suspension, bulk sterilization and process related to Brinzolamide product.
- **Frequency:** Shall be performed at least10 times in solution, suspension, bulk sterilization and 6 times in process related to Brinzolamide product.
- **Filling machine door no. to be opened during intervention:** NA
- **Activity perform during intervention:** This intervention is to be executed through glove port with the sterile forceps kept under LAF.
- **Rationale:** During review of filling process this new type of intervention is identified and proposed to be simulated during the media fill. Contamination risk of this intervention in the filling process will be evaluated with the number of times proposed.

15. Correction of cap pick and place assembly.

- **Intervention type:** Routine intervention.
- **Duration of time:** Shall be performed for maximum 3 minutes.
- **Process applicable:** Solution, suspension, bulk sterilization and process related to Brinzolamide product.
- **Frequency:** Shall be performed at least10 times in solution, suspension, bulk sterilization and 6 times in process related to Brinzolamide product.
- **Filling machine door no. to be opened during intervention:** NA
- **Activity performs during intervention:** This intervention is to be executed through glove port with the sterile forceps kept under LAF.
- **Rationale:** During review of filling process this new type of intervention is identified and proposed to be simulated during the media fill. Contamination risk of this intervention in the filling process will be evaluated with the number of times proposed.

16. Correction of rejection station.

- **Intervention type:** Routine intervention.
- **Duration of time:** Shall be performed for maximum 3 minutes.
- **Process applicable:** Solution, suspension, bulk sterilization and process related to Brinzolamide product.
- **Frequency:** Shall be performed at least 5 times in solution, suspension, bulk sterilization and 4 times in process related to Brinzolamide product.
- **Filling machine door no. to be opened during intervention:** NA
- **Activity perform during intervention:** This intervention is to be executed through glove port with the sterile forceps kept under LAF.
- **Rationale:** During review of filling process this new type of intervention is identified and proposed to be simulated during the media fill. Contamination risk of this intervention in the filling process will be evaluated with the number of times proposed.

17. Environmental monitoring to be perform through settle plate /air sampling.

- **Intervention type:** Routine intervention.

- **Duration of time:** Shall be performed for maximum 3 minutes.
- **Process applicable:** Solution, suspension, bulk sterilization and process related to Brinzolamide product.
- **Frequency:** Shall be performed at least 8 times in solution, suspension, bulk sterilization and for process related to Brinzolamide product.
- **Filling machine door no. to be opened during intervention:** E/FD-011 AND E/FD-012.
- **Activity perform during intervention:** hand sanitization to be done, Guard door no. E/FD-011 and E/FD - 012 to be opened and intervention of environmental monitoring by settle plate and air sampling to be done, finally filling machine guard door E/FD-011 and E/FD-012 to be closed.
- **Rationale:**
  - ✓ The duration of process simulation should generally be not less than the actual production process to best simulate the contamination risk introduced to the filling activity during environmental monitoring activity.
  - ✓ Based upon the trend of 10 media fill batches and 10 production batches data obtained, it is proposed to complete the intervention environmental monitoring activity within 3 minutes. Based on the proposed maximum production batch size number of times is finalized to simulate during media fill.

18. Walking beam overload.

- **Intervention type:** Routine intervention.
- **Duration of time:** Shall be performed for maximum 3 minutes.
- **Process applicable:** Solution, suspension, bulk sterilization and process related to Brinzolamide product.
- **Frequency:** Shall be performed at least 10 times in solution, suspension, bulk sterilization and at least 6 times for process related to Brinzolamide product.
- **Filling machine door no. to be opened during intervention:** NA
- **Activity perform during intervention:** This intervention is to be executed through glove ports with the sterile forceps kept under LAF.
- **Rationale:**
  - ✓ The duration of process simulation should generally be not less than the actual production process to best simulate the contamination risk introduced to the filling activity during walking beam over load.
  - ✓ Based upon the trend of 10 media fill batches and 10 production batches data obtained, it is proposed to complete the intervention walking beam overload within 3 minutes. Based on the proposed maximum production batch size number of times is finalized to simulate during media fill.

19. Minor machine adjustment.

- **Intervention type:** Routine intervention.
- **Duration of time:** Shall be performed for maximum 3 minutes.
- **Process applicable:** Solution, suspension, bulk sterilization and process related to Brinzolamide product.
- **Frequency:** Shall be performed at least 2 times in solution, suspension, bulk sterilization and process related to Brinzolamide product.
- **Filling machine door no. to be opened during intervention:** NA
- **Activity perform during intervention:** This intervention is to be executed through glove ports with the sterile forceps kept under LAF.
- **Rationale:**
  - ✓ The duration of process simulation should generally be not less than the actual production process to best simulate the contamination risk introduced to the filling activity during minor machine adjustment.
  - ✓ Based upon the trend of 10 media fill batches and 10 production batches data obtained, it is proposed to complete the intervention minor machine adjustment activity within 3 minutes. Based on the proposed maximum production batch size number of times is finalized to simulate during media fill.

20. Lunch / Dinner break.

- **Intervention type:** Routine intervention.
- **Duration of time:** Break for 45 minutes for lunch/Dinner.
- **Process applicable:** Solution, suspension, bulk sterilization and process related to Brinzolamide product.

- **Frequency:** Shall be performed at least 2 times in solution, suspension, bulk sterilization and at least 6 times for process related to Brinzolamide product.
- **Filling machine door no. to be opened during intervention:** NA
- **Activity perform during intervention:** During this intervention oprator shall take the lunch / dinner and night break tea.
- **Rationale:** Based upon the 10 actual production data and media fill it can be concluded that the maximum time break can be taken for 45 minutes and frequency decided to access the potential for a unit of during actual production data from the process simulation can provide useful information for processing line evaluation.

21. Operator fatigue.

- **Intervention type:** Routine intervention.
- **Duration of time:** For 10 minutes.
- **Process applicable:** Solution, suspension, bulk sterilization and process related to Brinzolamide product.
- **Frequency:** Shall be performed at least 1 times in solution, suspension, bulk sterilization and process related to Brinzolamide product.
- **Filling machine door no. to be opened during intervention:** NA
- **Activity perform during intervention:** Single operator after working inside filling area for more than 4 hours is considered as filling fatigue. During media fill this situation is also simulated for 10 minutes as is expected during production batch as well.

- **Rationale:**

  - ✓ The duration of process simulation should generally be not less than the actual production process to best simulate the contamination risk introduced to the filling activity during operator fatigue.
  - ✓ Based upon the trend of 10 media fill batches and 10 production batches data obtained, it is proposed to complete the intervention of operator fatigue for 10 minutes. Based on the proposed maximum production batch size number of times is finalized to simulate during media fill.

22. Sift change over.

- **Intervention type:** Routine intervention.
- **Duration of time:** Shall be performed for 10 minutes.
- **Process applicable:** Solution, suspension, bulk sterilization and process related to Brinzolamide product.
- **Frequency:** Shall be performed at least 2 times in solution, suspension, bulk sterilization and process related to Brinzolamide product.
- **Filling machine door no. to be opened during intervention:** NA
- **Activity perform during intervention:** During this intervention job handover is done by one operator to next sift operator, Status of batch is informed as a part of job handover to the next operator in next shift.
- **Rationale:**

  - ✓ The duration of process simulation should generally be not less than the actual production process to best simulate the contamination risk introduced to the filling activity during shift changeover.
  - ✓ Based upon the trend of 10 media fill batches and 10 production batches data obtained, it is proposed to complete the intervention to shift changeover for 10 minutes. Based on the proposed maximum production batch size number of times is finalized to simulate during media fill.
  - ✓ Production batch runs in 3 shifts ,so , shift change over is to be simulated in media fill for 2 times.

23. Aseptic dissembling of filling machine parts after completion of filling.

- **Intervention type:** Routine intervention.
- **Duration of time: S**hall be performed for 01 hours and 30 minutes.
- **Process application:** Solution, suspension, bulk sterilization and process related to Brinzolamide product.

- **Frequency:** Shall be performe at 1 time at the end of filling in solution, suspension, bulk sterilization and process related to Brinzolamide product.
- **Filling Machine door no. to be opened during intervention:** E/FD-001, E/FD-002, E/FD-004,E/FD-005, E/FD-007, E/FD-008, E/F-009,E/FD-010,E/FD-011,E/FD-012,E/D-014,E/FD-015. According to the activity filling machine door to be open and two filling machine door shall be open maximum for 20 minutes during assembling.
- **Activity perform during intervention:** After completion of filling activity, dissembling of filling change parts to be done, during this intervention two filling machine door to be kept open maximum for 20 minutes at a stretch.
- **Rationale:** As suggested by regulatory inspector, earlier this intervention was not simulated during fill and the impect of this intervention on production batch was not evaluated. Hence, this new type of intervention is identified and proposed to be simulated during the media fill. Contamination risk of this intervention in the filling process will be evaluated.

24. Post cleaning of filling machine after completion of filling.

- **Intervention type:** Routine intervention.
- **Duration of time:** Shall be performed for 45 minutes.
- **Process application:** Solution, suspension, bulk sterilization and process related to Brinzolamide product.
- **Frequency:** Shall be perform at 1 time at the end of filling in solution, suspension, bulk sterilization and process related to Brinzolamide product.
- **Filling Machine door no. to be opened during intervention:** E/FD-001, E/FD-002, E/FD-004, E/FD-005, E/FD-007, E/FD-008, E/F-009,E/FD-010,E/FD-011,E/FD-012,E/D-014,E/FD-015. According to the activity filling machine door to be open and two filling machine door shall be open maximum for 20 minutes during assembling.
- **Activity perform during intervention:** After completion of dissembling activity, post cleaning activity to be done. During this intervention two filling machine door to be kept open maximum for 20 minutes at a stretch, post cleaning intervention or activity to be performed under controlled condition and approved procedures.
- **Rationale:** During review of filling process this new type of intervention is identified and proposed to be simulated during the media fill. Contamination risk of this intervention in the filling process will be evaluated with the number of times proposed.

24. Post cleaning of filling machine after completion of filling.

- **Intervention type:** Routine intervention.
- **Duration of time : S**hall be performed for 45 minutes.
- **Process application:** Solution, suspension, bulk sterilization and process related to Brinzolamide product.
- **Frequency:** Shall be performe at 1 time at the end of filling in solution, suspension, bulk sterilization and process related to Brinzolamide product.
- **Filling Machine door no. to be opened during intervention:** E/FD-001, E/FD-002, E/FD-004,E/FD-005, E/FD-007, E/FD-008, E/F-009,E/FD-010,E/FD-011,E/FD-012,E/D-014,E/FD-015. According to the activity filling machine door to be open and two filling machine door shall be open maximum for 20 minutes during assembling.
- **Activity perform during intervention:** After completion of filling activity, dissembling of filling change parts to be done, during this intervention two filling machine door to be kept open maximum for 20 minutes at a stretch.
- **Rationale:** As suggested by regulatory inspector, earlier this intervention was not simulated during fill and the impect of this intervention on production batch was not evaluted. Hence, this new type of intervention is identified and proposed to be simulated during the media fill. Contamination risk of this intervention in the filling process will be evaluated.

25. Correction of bottle blockage in bottle chute.

- **Intervention type:** Non-Routine intervention.
- **Duration of time:** Shall be performed for maximum 3 minutes.
- **Process applicable:** Solution, suspension, bulk sterilization and process related to Brinzolamide product.

- **Frequency:** Shall be performed at least 2 times in solution, suspension, bulk sterilization and 1 times in process related to Brinzolamide product.
- **Filling machine door no. to be opened during intervention:** E/FD-004.
- **Activity perform during intervention:** Hand sanitization to be done, Guard door no.E/FD-004 to be opened and intervention of clearing bottle blockage in bottle chute to be done, finally filling machine guard door E/FD to be closed.
- **Rationale:** During review of filling process this new type of intervention is identified and proposed to be simulated during the media fill. Contamination risk of this intervention in the filling process will be evaluated with the number of times proposed.

26. Correction of bottle blockage at in feed guide of bottle.

- **Intervention type:** Non-Routine intervention.
- **Duration of time:** Shall be performed for 3 minutes.
- **Process applicable:** Solution, suspension, bulk sterilization and process related to Brinzolamide product.
- **Frequency:** Shall be performed at least 1 time in solution, suspension, bulk sterilization and process related to Brinzolamide product.
- **Filling machine door no. to be opened during intervention:** E/FD-003 and E/FD-013.
- **Activity perform during intervention:** Hand sanitization to be done, Guard door no. E/FD-003 and E/FD-013 to be opened and intervention of clearing bottle blockage in feed guide of bottle to be done, finally filling machine guard door E/FD-003 and E/FD-013 to be closed.
- **Rationale:** During review of filling process this new type of intervention is identified and proposed to be simulated during the media fill. Contamination risk of this intervention in the filling process will be evaluated with the number of times proposed.

27. Removal of fallen bottle on working beam from discharge chute.

- **Intervention type:** Non-Routine intervention.
- **Duration of time:** Shall be performed for maximum 3 minutes.
- **Process applicable:** Solution, suspension, bulk sterilization and process related to Brinzolamide product.
- **Frequency:** Shall be performed at least 2 times in solution, suspension, bulk sterilization and at least 1 time for process related to Brinzolamide product.
- **Filling machine door no. to be opened during intervention:** E/FD-004 and E/FD-0005, E/FD-006, E/FD-007. Filling machine guard door need to be open to perform the intervention.
- **Activity perform during intervention:** Hand sanitization to be done, Guard door no. E/FD-004, E/FD-005, E/FD-006, and E/FD-007 to be opened and intervention of removal of fallen bottles on walking beam from discharge chute to be done , finally filling machine guard door E/FD-004 E/FD-005, E/FD-006, and E/FD-007 to be closed.
- **Rationale:** During review of filling process this new type of intervention is identified and proposed to be simulated during the media fill. Contamination risk of this intervention in the filling process will be evaluated with the number of times proposed.

28. Removal of jammed filled and capped bottle at out feed of capping machine.

- **Intervention type:** Non-Routine intervention.
- **Duration of time:** Shall be performed for maximum 3 minutes.
- **Process applicable:** Solution, suspension, bulk sterilization and process related to Brinzolamide product.
- **Frequency:** Shall be performed at least 2 times in solution, suspension, bulk sterilization and at least 1 time for process related to Brinzolamide product.
- **Filling machine door no. to be opened during intervention:** E/FD-004, FD-0005, E/FD-006, E/FD-007.
- **Activity perform during intervention:** Hand sanitization to be done, Guard door no. E/FD-004, E/FD-005, E/FD-006, and E/FD-007 to be opened and intervention of removal of jammed filled and capped bottles at out feed of capping machine to be done , finally filling machine guard door E/FD-004 E/FD-005, E/FD-006, and E/FD-007 to be closed.
- **Rationale:** During review of filling process this new type of intervention is identified and proposed to be simulated during the media fill. Contamination risk of this intervention in the filling process will be evaluated with the number of times proposed.

29. Correction of dropper in dropper vibratory bowl.

- **Intervention type:** Non-Routine intervention.
- **Duration of time:** Shall be performed for maximum 2 minutes.
- **Process applicable:** Solution, suspension, bulk sterilization and process related to Brinzolamide product.
- **Frequency:** Shall be performed at least 2 times in solution, suspension, bulk sterilization and at least 1 time for process related to Brinzolamide product.
- **Filling machine door no. to be opened during intervention:** E/FD-011.
- **Activity perform during intervention:** Hand sanitization to be done, Guard door no. E/FD-011 to be opened and intervention of correction of dropper in dropper vibratory bowl to be done , finally filling machine guard door E/FD-011 to be closed.
- **Rationale:** During review of filling process this new type of intervention is identified and proposed to be simulated during the media fill. Contamination risk of this intervention in the filling process will be evaluated with the number of times proposed.

30. Correction of dropper movement in dropper chute.

- **Intervention type:** Routine intervention.
- **Duration of time:** Shall be performed for maximum 3 minutes.
- **Process applicable:** Solution, suspension, bulk sterilization and process related to Brinzolamide product.
- **Frequency:** Shall be performed at least 2 times in solution, suspension, bulk sterilization and at least 1 time for process related to Brinzolamide product.
- **Filling machine door no. to be opened during intervention:** E/FD-011.
- **Activity perform during intervention:** During this intervention correction of dropper movement in dropper chute, when this intervention is occurred handle through open the filling machine guard door no. E/FD-011 with the help of sterilized forcep.
- **Rationale:** During review of filling process this new type of intervention is identified and proposed to be simulated during the media fill. Contamination risk of this intervention in the filling process will be evaluated with the number of times proposed.

31. Correction of dropper in dropper pick and place assembly.

- **Intervention type:** Noun-Routine intervention.
- **Duration of time:** Shall be performed for maximum 3 minutes.
- **Process applicable:** Solution, suspension, bulk sterilization and process related to Brinzolamide product.
- **Frequency:** Shall be performed at least 2 times in solution, suspension, bulk sterilization and at least 1 time for process related to Brinzolamide product.
- **Filling machine door no. to be opened during intervention:** E/FD-005.
- **Activity perform during intervention:** During this intervention correction of dropper movement in dropper chute, when this intervention is occurred handle through open the filling machine guard door no. E/FD-011 with the help of sterilized forcep.
- **Rationale:** During review of filling process this new type of intervention is identified and proposed to be simulated during the media fill. Contamination risk of this intervention in the filling process will be evaluated with the number of times proposed.

32. Corrective of cap movement in cap vibratory bowl.

- **Intervention type:** Non-Routine intervention.
- **Duration of time:** Shall be performed for maximum 2 minutes.
- **Process applicable:** Solution, suspension, bulk sterilization and process related to Brinzolamide product.
- **Frequency:** Shall be performed at least 2 times in solution, suspension, bulk sterilization and at least 1 time for process related to Brinzolamide product.
- **Filling machine door no. to be opened during intervention:** E/FD-010.
- **Activity perform during intervention:** Hand sanitization to be done, Guard door no. E/FD-010 to be opened and intervention of correction of cap movement in cap vibratory bowl to be done, finally filling machine guard door E/FD-010 to be closed.
- **Rationale:** During review of filling process this new type of intervention is identified and proposed to be simulated during the media fill. Contamination risk of this intervention in the filling process will be evaluated with the number of times proposed.

33. Correction of cap movement in cap chute.

- **Intervention type:** Non- Routine intervention.
- **Duration of time:** Shall be performed for maximum 3 minutes.
- **Process applicable:** Solution, suspension, bulk sterilization and process related to Brinzolamide product.
- **Frequency:** Shall be performed at least 2 times in solution, suspension, bulk sterilization and at least 1 time for process elated to Brinzolamide product.
- **Filling machine door no. to be opened during intervention:** E/FD-010.
- **Activity perform during intervention:** Hand sanitization to be done, Guard door no. E/FD-010 to be opened and intervention of correction of cap movement in cap vibratory bowl to be done, finally filling machine guard door E/FD-010 to be closed.
- **Rationale:** During review of filling process this new type of intervention is identified and proposed to be simulated during the media fill. Contamination risk of this intervention in the filling process will be evaluated with the number of times proposed.

34. Correction of cap in cap pick and place assembly.

- **Intervention type:** Routine intervention.
- **Duration of time:** Shall be performed for maximum 2 minutes.
- **Process applicable:** Solution, suspension, bulk sterilization and process related to Brinzolamide product.
- **Frequency:** Shall be performed at least 2 times in solution, suspension, bulk sterilization and at least 1 time for process related to Brinzolamide product.
- **Filling machine door no. to be opened during intervention:** E/FD-005, E/FD-006, E/FD-007.
- **Activity perform during intervention:** Hand sanitization to be done, Guard door no. E/FD-005, E/FD-006, E/FD-007to be opened and intervention of correction of cap in cap pick place assembly to be done, finally filling machine guard door E/FD-005, E/FD-006, E/FD-007to be closed.
- **Rationale:** During review of filling process this new type of intervention is identified and proposed to be simulated during the media fill. Contamination risk of this intervention in the filling process will be evaluated with the number of times proposed.

35. Correction of rejection station.

- **Intervention type:** Routine intervention.
- **Duration of time:** Shall be performed for maximum 3 minutes.
- **Process applicable:** Solution, suspension, bulk sterilization and process related to Brinzolamide product.
- **Frequency:** Shall be performed at least 1 times in solution, suspension, bulk sterilization and process related to Brinzolamide product.
- **Filling machine door no. to be opened during intervention:** E/FD-006, E/FD-007.
- **Activity perform during intervention:** Hand sanitization to be done, Guard door no.E/FD-006, E/FD-007to be opened and intervention of correction of rejection station to be done, finally filling machine guard door E/FD-006, E/FD-007 to be closed.
- **Rationale:** During review of filling process this new type of intervention is identified and proposed to be simulated during the media fill. Contamination risk of this intervention in the filling process will be evaluated with the number of times proposed.

36. Walking beam overload.

- **Intervention type:** Non-Routine intervention.
- **Duration of time:** Shall be performed for maximum 3 minutes.
- **Process applicable:** Solution, suspension, bulk sterilization and process related to Brinzolamide product.
- **Frequency:** Shall be performed at least 2 times in solution, suspension, bulk sterilization and at least 1 time for process related to Brinzolamide product.
- **Filling machine door no. to be opened during intervention:** E/FD-004, E/FD-005, E/FD-006.
- **Activity perform during intervention:** Hand sanitization to be done, Guard door no. E/FD-004, E/FD-005, E/FD-006 to be opened and intervention of walking beam overload to be done, finally filling machine guard door E/FD-004, E/FD-005, E/FD-006 to be closed.

- **Rationale:** During review of filling process this new type of intervention is identified and proposed to be simulated during the media fill. Contamination risk of this intervention in the filling process will be evaluated with the number of times proposed.

37. Minor machine adjustment.

- **Intervention type:** Non- Routine intervention.
- **Duration of time:** Shall be performed for maximum 3 minutes.
- **Process applicable:** Solution, suspension, bulk sterilization and process related to Brinzolamide product.
- **Frequency:** Shall be performed at least 1 times in solution, suspension, bulk sterilization and process related to Brinzolamide product.
- **Filling machine door no. to be opened during intervention:** All doors shall be opened according to which side minor machine intervention occurred.
- **Activity perform during intervention:** During the intervention as minor machine adjustment open the doors according to which side or location intervention occurred. To rectify the machine adjustment use sterile forceps.
- **Rationale:** During review of filling process this new type of intervention is identified and proposed to be simulated during the media fill. Contamination risk of this intervention in the filling process will be evaluated with the number of times proposed.

38. Machine breakdown activities shall be performed for 2 hours.

- **Intervention type:** Non- Routine intervention.
- **Duration of time:** Shall be performed for maximum 2 Hours.
- **Process applicable:** Solution, suspension, bulk sterilization and process related to Brinzolamide product.
- **Frequency:** Shall be performed at least 1 times in solution, suspension, bulk sterilization and process related to Brinzolamide product.
- **Filling machine door no. to be opened during intervention:** To be handle this intervention of machine breakdown all door can be opened, which is applicable to the machine from where the breakdown can be attended, two guard doors shall be kept open for maximum 20 minutes.
- **Activity perform during intervention:** During the intervention as machine breakdown activity for 2 hours which door required is to be open to resolve the intervention activity shall be performed for 2 hours.
- **Rationale:** taken to demonstrate the ability of engineer to correct problem without contaminating the filling process. Based upon the actual production data and media fill it can be concluded the maximum time activity performed for 2 hours.

39. Realignment of filling needle.

- **Intervention type:** Non- Routine intervention.
- **Duration of time:** Shall be performed for maximum 3 minutes.
- **Process applicable:** Solution, suspension, bulk sterilization and process related to Brinzolamide product.
- **Frequency:** Shall be performed at least 1 times in solution, suspension, bulk sterilization and process related to Brinzolamide product.
- **Filling machine door no. to be opened during intervention:** E/ED-005.
- **Activity perform during intervention:** Hand sanitization to be done, Guard door no. E/FD-005 to be opned and intervention of realignment of filling needle to be done, finally filling machine guard door E/FD-005 to be closed.
- **Rationale:** Based upon the 10 actual production data and meedia fill it can be concluded that the maximum time activity performed for maximum 3 minutes and frequency decided to be access the potential for a unit of drug product during actual production data from the process simulation can provide useful information for processing line evalution.

40. Realingnment of filling needle.

- **Intervention type:** Non- Routine intervention.

- **Duration of time:** Shall be performed for maximum 3 minutes.
- **Process applicable:** Solution, suspension, bulk sterilization and process related to Brinzolamide product.
- **Frequency:** Shall be performed at least 1 times in solution, suspension, bulk sterilization and process related to Brinzolamide product.
- **Filling machine door no. to be opened during intervention:** NA.
- **Activity perform during intervention:** This intervention is to be executed through glove ports with the sterile forceps kept under LAF.
- **Rationale:**

  - ✓ The duration of process simulation should generally be not less than actual production process to best simulates the contamination risk introduced to the filling activity during realignment of filling needle.
  - ✓ Based upon the trend of 10 media fill batches and 10 production batches data and obtained, it is proposed to complete the intervention realignment of filling needle within 3 minutes. Based on the proposed maximum production batch size number of times is finalized to simulate during media fill.

41. Ahu of filling area switch off for 3 minutes.

- **Intervention type:** Non- Routine intervention.
- **Duration of time:** Shall be performed for maximum 3 minutes.
- **Process applicable:** Solution, suspension, bulk sterilization and process related to Brinzolamide product.
- **Frequency:** Shall be performed at least 1 times in solution, suspension, bulk sterilization and process related to Brinzolamide product.
- **Filling machine door no. to be opened during intervention:** NA.
- **Activity perform during intervention:** During This intervention as AHU of filling area shut down foe 3 minutes to demonstrate the area. AHU is monitored or controlled through BMS system.
- **Rationale:**

  - ✓ The duration of process simulation should generally be not less than actual production process to best simulates the contamination risk introduced to the filling activity during AHU of filling switched off for 3 minutes.
  - ✓ Based upon the trend of 10 media fill batches data and obtained, it is proposed to complete the intervention AHU of filling area switched off for 3 minutes.

42. Power supply to the machine to be switched off for 30 minutes with LAF is on.

- **Intervention type:** Non- Routine intervention.
- **Duration of time:** Shall be performed for maximum 30 minutes.
- **Process applicable:** Solution, suspension, bulk sterilization and process related to Brinzolamide product.
- **Frequency:** Shall be performed at least 1 times in solution, suspension, bulk sterilization and process related to Brinzolamide product.
- **Filling machine door no. to be opened during intervention:** NA.
- **Activity perform during intervention:** During this intervention, power supply of filling machine to be switched off and LAF of filling machine is kept in ON condition.

Rationale: Based upon the trend of 10 media fill batches data and obtained, it is proposed to complete the intervention power supply to the machine to be switched off for 30 minutes with LAF in ON condition.

43. Area pressure drop below set point foe 2 minutes.

- **Intervention type:** Non- Routine intervention.
- **Duration of time:** Shall be performed for maximum 2 minutes.
- **Process applicable:** Solution, suspension, bulk sterilization and process related to Brinzolamide product.

- **Frequency:** Shall be performed at least 1 times in solution, suspension, bulk sterilization and process related to Brinzolamide product.
- **Filling machine door no. to be opened during intervention:** NA.
- **Activity perform during intervention:** During this intervention, filling area differential pressure w.r.t to adjacent area dropped below set points for 2 minutes.
- **Rationale:** Based upon the trend of 10 media fill batches data, it can be concluded that the maximum time of filling area differentaial pressure w.r.t to adjacent area dropped bellow set points for maximum 2 minutes.

44. Filling area door open for 2 minutes.

- **Intervention type:** Non- Routine intervention.
- **Duration of time:** Shall be performed for maximum 2 minutes.
- **Process applicable:** Solution, suspension, bulk sterilization and process related to Brinzolamide product.
- **Frequency:** Shall be performed at least 1 times in solution, suspension, bulk sterilization and process related to Brinzolamide product.
- **Filling machine door no. to be opened during intervention:** NA.
- **Activity perform during intervention:** During this intervention, filling area door is opened for 2 minutes to simulate activites like transfer of mobile LAF and personal movement.
- **Rationale:** Based upon the 10 actual production data and 10 media fill batches, it is concluded that the maximum time filling area door can be kept opned for maximum 2 minutes to evaluate the contamination risk to the product.

45. Opening of filling machine door for 20 minutes.

- **Intervention type:** Non- Routine intervention.
- **Duration of time:** Shall be performed for maximum 20 minutes.
- **Process applicable:** Solution, suspension, bulk sterilization and process related to Brinzolamide product.
- **Frequency:** Shall be performed at least 1 times in solution, suspension, bulk sterilization and process related to Brinzolamide product.
- **Filling machine door no. to be opened during intervention:** E/FD-004 and E/FD-005.
- **Activity perform during intervention:** During the intervention two guard doors no.as E/FD-004 and E/FD-005 of filling machine to be kept open for maximum 20 minutes during disassembling and do not move unnecessarily inside the filling area.
- **Rationale:** During review of filling process this new type of intervention is identified and proposed to be simulated during the media fill. Contamination risk of this intervention in the filling process will be evaluated with the number of times proposed.

46. Change of gloves during intervention.

- **Intervention type:** Non- Routine intervention.
- **Duration of time:** Shall be performed for maximum 2 minutes.
- **Process applicable:** Solution, suspension, bulk sterilization and process related to Brinzolamide product.
- **Frequency:** Shall be performed at least 1 times in solution, suspension, bulk sterilization and process related to Brinzolamide product.
- **Filling machine door no. to be opened during intervention:** NA.
- **Activity perform during intervention:** During this intervention change the outer gloves in entery filling room-III.
- **Rationale:** Based upon the 10 actual production data and media fill it can be concluded that the maximum time activity performed for maximum 2 minutes and frequency decided to access the potential for a unit of drug product during actual production data from the process simulation can provide useful information for processing line evalution.

47. Filling with single head.

- **Intervention type:** Non- Routine intervention.

- **Duration of time:** Shall be performed for maximum 2 minutes.
- **Process applicable:** Solution, suspension, bulk sterilization and process related to Brinzolamide product.
- **Frequency:** Shall be performed at least 1 times in solution, suspension, bulk sterilization and process related to Brinzolamide product.
- **Filling machine door no. to be opened during intervention:** NA.
- **Activity perform during intervention:** During this intervention change the outer gloves in entery filling room-III.

- **Rationale:** Based upon the 10 actual production data and media fill it can be concluded that the maximum time activity performed for maximum 2 minutes and frequency decided to access the potential for a unit of drug product during actual production data from the process simulation can provide useful information for processing line evalution.

48. Increase in number of person's more than routine up to maximum 7 persons.

- **Intervention type:** Worst case intervention.
- **Duration of time:** Shall be performed for maximum 10 minutes.
- **Process applicable:** Solution, suspension, bulk sterilization and process related to Brinzolamide product.
- **Frequency:** Shall be performed at least 1 times in solution, suspension, bulk sterilization and process related to Brinzolamide product.
- **Filling machine door no. to be opened during intervention:** NA.
- **Activity perform during intervention:** During this intervention 7 person present in filling room and perform the filling activity. Representative from verios department shall be allowed inside the area.
- **Rationale:** Based upon the 10 actual production data and media fill it can be concluded that the maximum time activity performed for 10 minutes and frequency decided to access the potential for a unit of drug product during actual production data from the process simulation can provide useful information for processing line evalution.

49. Filling with the single head.

- **Intervention type:** Worst case intervention.
- **Duration of time:** Shall be performed for maximum 1 hour.
- **Process applicable:** Solution, suspension, bulk sterilization and process related to Brinzolamide product.
- **Frequency:** Shall be performed at least 1 times in solution, suspension, bulk sterilization and process related to Brinzolamide product.
- **Filling machine door no. to be opened during intervention:** NA.
- **Activity perform during intervention:** In case of jam of piston or pump perform the filling with single pump and piston.
- **Rationale:** During revew of filling process this new type of intervention identified and proposed to be simulated during the media fill. Contamination risk of this intervention in the filling process will be evaluated with the number of times proposed.

50. Replacement of the filling nedle and piston pump during media filling by opening the filling machine guard door.

- **Intervention type:** Worst case intervention.
- **Duration of time:** Time not stableished.
- **Process applicable:** Solution, suspension, bulk sterilization and process related to Brinzolamide product.
- **Frequency:** Shall be performed at least 1 times in solution, suspension, bulk sterilization and process related to Brinzolamide product.
- **Filling machine door no. to be opened during intervention:** E/FD-004, E/FD-005 and E/FD-012 and two filling machine door shall be kept open for maximum 20 minutes.
- **Activity perform during intervention:** In case of jam of piston or pump replacement of filling needle and piston pump to be done.

- **Rationale:** During revew of filling process this new type of intervention is identified and proposed to be simulated during the media fill. Contamination risk of this intervention in the filling process
- will be evaluated with the number of times proposed.

51. Change in the sterilizing grade filter during media filling for holding tank.

- **Intervention type:** Worst case intervention.
- **Duration of time:** Time not stableished.
- **Process applicable:** Solution and suspension process.
- **Frequency:** Shall be performed at least 1 times in solution and suspension process.
- **Filling machine door no. to be opened during intervention:** NA
- **Activity perform during intervention:** In case of jam of filter choke during filtration and filtration not complete than replace the choked filter with another sterilized aseptically.
- **Rationale:** During revew of filling process this new type of intervention is identified and proposed to be simulated during the media fill. Contamination risk of this intervention in the filling process will be evaluated with the number of times proposed.